PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference N.88387A - GWM	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/GB2004/001651	International filing date *(day/month/year)* 15.04.2004	Priority date *(day/month/year)* 15.04.2003
International Patent Classification (IPC) or national classification and IPC A61K47/28, A61K47/14, A61K47/10, A61K38/28, A61K38/23		
Applicant AXCESS LIMITED et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
15.02.2005	09.03.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Paul Soto, R Telephone No. +49 89 2399-7346

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/001651

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-16 as originally filed

Claims, Numbers

1-25 as originally filed

Drawings, Sheets

1/3-3/3 as originally filed

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/001651

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 25 (industrial applicability)

because:

☒ the said international application, or the said claims Nos. 25 (industrial applicability) relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2-11, 16, 18-24
	No:	Claims	1, 12-15, 17, 25
Inventive step (IS)	Yes:	Claims	2-11, 16, 18-24
	No:	Claims	1, 12-15, 17, 25
Industrial applicability (IA)	Yes:	Claims	1-15, for 16-25 see separate sheet
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. Claim 25 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

2. Reference is made to the following documents:
   - **D1**: DATABASE WPI Section Ch, Week 198149 Derwent Publications Ltd., London, GB; Class B01, AN 1981-90325D XP002292155 & JP 56 138168 A (TEIJIN LTD) 28 October 1981
   - **D2**: WO 96/40192 A (AVMAX INC ; BENET LESLIE Z (US); BENET REED M (US); WACHER VINCENT J () 19 December 1996
   - **D3**: WO 97/33531 A (STERN WILLIAM ; UNIGENE LAB INC (US); GILLIGAN JAMES P (US)) 18 September 1997
   - **D4**: WO 97/21448 A (DULLATUR LIMITED ; BYRNE WILLIAM (IE); DRISCOLL CAITRIONA M O (IE); CO) 19 June 1997

   If not indicated otherwise, the relevant passages are those mentioned in the International Search Report.

3. The present application according to **claim 1** relates to a pharmaceutical composition comprising a mixture of: a) an active macromolecular principle, b) a non-conjugated bile acid or salt, and c) an additive chosen from propyl gallate, butyl hydroxy anisole (BHA) and analogues and derivatives thereof, or mixtures thereof. **Claims 16** is directed to the use in a pharmaceutical composition of a non-conjugated bile acid or salt, together with an additive chosen from propyl gallate and BHA and analogues and derivatives thereof, or mixtures thereof as an enhancer for the absorption of macromolecules across the intestinal wall. **Claim 17** covers the same scope as claim 16 but is drafted in the second-medical use

format. **Claim 24** relates to a method of enhancing the absorption of an active macromolecular principle in a patient, comprising administering to said patient the previously defined composition. Finally, **claim 25** is directed to a method of treating a patient suffering from a condition or disease.

4. The present application does not meet the requirements of the PCT with respect to novelty (Art. 33(2)).

D1 discloses pharmaceutical compositions comprising Vitamin D3 (hydroxycholecalciferol), a bile acid derivative such as deoxychoilc or chendeoxycholic acid, and an antioxidant such as propyl gallic acid and butyl hydroxyanisole. However, the effect of enhancing the absorption of macromolecules across the intestinal wall is not mentioned. This is regarded as novelty destroying for present claims 1, 12-15, 17 and 25.

D2 discloses cyclosporin compositions with improved bioavailability due to the addition of an essential oil. In a specific composition (see table 4) BHA and bile salt of deoxycholic acid of glycholic acid are present. However, the BHA is present as an antioxidant. Thus, it is considered that the effect of enhancing the absorption of macromolecules is not disclosed for the mixture of BHA and bile salt. This document is regarded as novelty destroying for present claims 1, 12, 14, 15, 17 and 25.

5. The subject-matter of present claims 2-11, 16 and 18-24 is novel and meets also the requirements of inventive step (Art. 33(3) PCT).

D3 and **D4** appear to represent the closest prior art. They disclose pharmaceutical compositions of calcitonin or insulin as active compound, a bile acid or salt as absorption enhancer (such as chenodeoxycholic acid) and further agents such as, pH regulating agents, or an enzyme inhibitor for an improved bioavailability. The present application differs from the closest prior art in that the improved bioavalability is achieved by the addition of BHA or propyl gallate through an increase of the solubility of the bile acid.

Thus, the *problem* to be solved by the present application is regarded in the provision of alternative calcitonin or insulin compositions comprising a bile acid as absorption enhancer exhibiting an improved uptake of the macromolecules. The

solution provided by the present application is not rendered obvious by any prior art document either alone or in combination. No indication has been found which would prompt the skilled person to a composition with BHA or propyl gallate.

6.1. Claims 1-15 meet the criterion set forth in Article 33(4) PCT because their subject-matter is susceptible of industrial application.

6.2 For the assessment of the present claims 16-25 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VIII

Certain observations on the international application

7. Present claim 23 does not meet the requirements of Art. 6 PCT with respect to clarity. Said dependent claim refers back to claims 16 to 21 and to "the aromatic alcohol" whereas in claims 16-to 21 no aromatic alcohol is mentioned.